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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/937,322	12/20/2001	Maria Gabriella Santoro	10167-013-999	9500

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EXAMINER	
WILLIAMS, LEONARD M	
ART UNIT	**PAPER NUMBER**
1617	

DATE MAILED: 11/17/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/937,322	SANTORO ET AL.	
	Examiner	Art Unit	
	Leonard M. Williams	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 December 2001*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *37-78* is/are pending in the application.

4a) Of the above claim(s) *38,39,44,45,47,49,50,57-69 and 74-78* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *37,40-43,46,48,51-56,70-73 and 79* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Detailed Action

The preliminary amendment received 09/21/2001 canceling claims 1-36 and adding new claims 37-78 is acknowledged and entered. Claims 37-78 are to be considered on their merits.

Election/Restrictions

Claims 38-39, 44-45, 47, 49-50, and 57-69 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 7/28/2005. Claims 1-36 and 74-78 are cancelled. Claim 79 has been added by the amendment of 7/28/2005 and is entered. The examiner has considered the applicant's suggestion to examine claim 40 and 41 to include both the racemate and enantiomers of 4-tert-butyldimethylsilyloxy-cyclopent-2-en-1-one and has deemed it appropriate thus including claim 41 in the claim examination. Claims 37, 40-43, 46, 48, 51-56, 70-73 and 79 are currently pending.

The applicant's were required to elect a disorder species and compound species. The applicant's have chosen the disorder species to be disorders associated with Nf-κB and the compound species as 4-tert-butyldimethylsilyloxy-cyclopent-2-en-1-one.

The election/restriction is made final.

Claim Rejections - 35 USC § 112 Prevention Enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 37, 40-43, 46, 48, 51-56, 70-73 and 79 are rejected under 35 U.S.C. 1 12, first paragraph, because the specification, while being enabling for treating a disorder does not provide enablement for preventing a disorder. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The instant specification fails to provide information that would allow the skilled artisan to practice the instant invention without undue experimentation. Attention is directed to *In re Wands*, 8 USPQ2d 1400 (CAFC 1988) at 1404 where the court set forth the eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing *Ex parte Forman*, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors: (1) the nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the ad; (4) the predictability or unpredictability of the ad; (5) the breadth of the claims', (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

(1) The Nature of the Invention:

The rejected claims are drawn to a method for treating or preventing a disorder in a host, by administration to a host in need thereof, a therapeutically or prophylactically effective amount of a compound of the formula (a) or (b).

(2) Breadth of the Claims:

The instant claims embrace preventing or treating any disorder with any of the compounds of formula (a) or (b).

(3) Guidance of the Specification:

The guidance of the specification as to the prevention of a disorder is completely lacking. On page 9 paragraph 1 of the specification, it states "The treatment may be prophylactic or may be in respect of an existing condition." There is no evidence or example to indicate prevention of any.

(4) Working Examples:

Applicant does not provide any working examples for the prevention of a disorder in a host, by administration to a host in need thereof, a therapeutically or prophylactically effective amount of a compound of the formula (a) or (b).

(5) State/predictability of the Art:

The state of the art regarding treating a disorder is relatively high. However, the state of the art for prevention of a disorder is underdeveloped.

(6) The Quantity of Experimentation Necessary:

The instant claims read on the prevention of any disorder in a host, by administration to a host in need thereof, a therapeutically or prophylactically effective amount of a compound of the formula (a) or (b). As discussed above, the specification fails to provide sufficient support for completely protecting a host, by administration to a host in need thereof, a therapeutically or prophylactically effective amount of a compound of the formula (a) or (b). Applicant fails to provide information sufficient to practice the claimed invention, absent undue experimentation. Genetech, 108 F.3d at 1366 states that "a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion" and "patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable."

Accordingly the claims are evaluated as drawn to method for treating a disorder in a host, by administration to a host, in need thereof, a therapeutically effective amount of a compound of the formula (a) or (b).

Claim Rejections - 35 USC § 112 Scope of Enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 37, 40-43, 46, 48, 51-56, 70-73 and 79 are rejected under 35 U.S.C. 1 12, first paragraph, because the specification, while being enabling for methods of

treating a disorder involving inhibition of replication of HSV-1 and Sendai virus via the inhibition of Nf-kB and activation of HSF by administration of compounds of formula (a) or (b) does not reasonably provide enablement for "A method for treating...a disorder in a host, comprising administrating to a host in need thereof a therapeutically...effective amount of a compound of the formula (a) or (b)...". Specifically the disclosure does not enable one to treat all disorders associated with Nf-kB activation. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The instant specification fails to provide information that would allow the skilled artisan to practice the instant invention without undue experimentation. Attention is directed to *In re Wands*, 8 USPQ2d 1400 (CAFC 1988) at 1404 where the court set forth the eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing *Ex parte Forman*, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors: (1) the nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the ad; (4) the predictability or unpredictability of the ad; (5) the breadth of the claims', (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

(1) The Nature of the Invention:

The rejected claims are drawn to a method for treating a disorder in a host, by administration to a host in need thereof, a therapeutically effective amount of a compound of the formula (a) or (b).

(2) Breadth of the Claims:

The breadth of the claims are exceptionally broad encompassing a method of treating any disorder (and specifically disorders associated with Nf-κB activation) with any of the compounds of formula (a) or (b).

(3) Guidance of the Specification:

The guidance of the specification as to a method for treating a disorder in a host (and in particular disorders associated with Nf-κB activation), by administration to a host in need thereof, a therapeutically effective amount of a compound of the formula (a) or (b) is limited to the in vitro cell-based assays of examples 1-4 and the rat animal model for blood pressure determination of example 5.

(4) Working Examples:

The applicant provides working examples in the in vitro cell-based assays of examples 1-4 and the rat animal model for blood pressure determination of example 5. CTC8 is S-(-)-4-tert-butyldimethylsilyloxy-cyclopent-2-en-1-one, CTC7 is R-(+)-4-tert-butyldimethylsilyloxy-cyclopent-2-en-1-one and CTC1 is cyclopent-2-en-1-one.

Example 1 details the effect of CTC8, CTC7 and CTC1 on the activity of HSF and Nf-kB in human lymphoblastoid Jurkat T cells when stimulated with TPA which is a known inducer of Nf-kB. The experiment clearly indicates that when human lymphoblastoid Jurkat T cells are stimulated with TPA, after pre-treatment of the cells with varying concentrations of CTC8, CTC7 and CTC1, that there is an induction of HSF and an inhibition of Nf-kB transcription.

Example 2 details the effectiveness of CTC8 (4-tert-butyldimethylsilyloxy-cyclopent-2-en-1-one, CTC7 (4-tert-butyldimethylsilyloxy-cyclopent-2-en-1-one) and CTC1 on the inhibition of replication of Herpes simplex virus type 1 in human HEP-2 laryngeal carcinoma cells and monkey VERO cells. Additionally CTC8 was tested against the know HSV1 compound acyclovir for comparative effectiveness. The experiment indicates that CTC8 and CTC7 are inhibitors of HSV-1 virus replication in the cell lines, and that the effective doses required for inhibition of virus replication is below the LD-50 of the compounds on the cell lines tested.

Example 3 details the effectiveness of CTC8, CTC7 and CTC1 on the inhibition of Sendai virus in monkey kidney 37RC cells. The experiment indicates that CTC8 and CTC7 are inhibitors SV replication in the cell line tested.

Example 4 details the concentration-dependent inhibitory effect of CTC8 on nitrite formation in the iNOS mouse macrophage model. PG-J_2 (the natural cyclopentenone prostaglandin) was used for comparative activity against CTC8. The experiment indicates that CTC8 inhibits the formation of nitrites in a concentration-

dependent manner in the mouse macrophages of the cell line RAW264.7 when the cells are stimulated with γ-interferon and lipopolysacchride.

Example 5 details the effect of CTC8 on the blood pressure of male Wistar rats after intravenous infusion. CTC8 had no effect on blood pressure at doses from 60-1200μg/kg/min.

There are no additional animal models presented and no human data presented for the compounds.

(5) State/predictability of the Art:

The state of the art regarding the testing of a method for treating any disorder (and specifically disorders associated with Nf-κB activation) with any of the compounds of formula (a) or (b) is high.

(6) The Quantity of Experimentation Necessary:

The instant claims read on a method of treating any disorder (and specifically disorders associated with Nf-κB activation) with any of the compounds of formula (a) or (b). Applicant fails to provide information sufficient to practice the claimed invention, absent undue experimentation (i.e. experimenting with all disorders associated with Nf-kB activation by administering the compounds of formula (a) or (b)).

The examiner presents evidence that undue experimentation is required by example of the following references:

Bourteele et al. Constitutive Activation of the Transcription Factor NF-κB Results in Impaired Borna Disease Virus Replication, Journal of Virology, may 2005, pp. 6043-6051. Bouteele et al. teach on pages 6043-6044 that while in some viruses the activation of NF-κB supports viral replication, it is generally believed that NF-κB activation acts as an antviral response in infection via activation of IFN-α/β. In the abstract Bourteele et al. state that enhanced NF-κB activity in the presence of Borna disease virus lead to the induction of antiviral pathways resulting in reduced viral titers.

Gadjeva et al., A Role for NF-kB Subunits p50 and p65 in the Inhibition of Lipopolysacchride-Induced Shock, Journal of Immunology, 2004, pp 5786-5793. Gadjeva et al. teach, in the abstract, that NF-kB subunits p50 and p65 have critical inhibitory functions during the systemic response to LPS and that they may be essential in preventing mortality due to systemic inflammatory response. On page 5787, Gadjeva et al. teach that mice deficient in NF-κB when exposed to LPS exhibited increased susceptibility to LPS-induced shock.

Kumar et al., Nuclear factor-κB: its role in health and disease, Journal of Molecular Medicine, review, 3 June 2004, pages 434-448. Kumar et al. teach on page 434, the NF-κB transcription factors propmote well over 150 genes involved in a variety of cellular processes such as regulation of growth factors, apoptosis, stress response, immunoregulation, etc.

The papers presented above detail that the inhibition of Nf-κB can have positive or negative effects in the treatment of viral infections based upon what virus is being

treated. One would have no a priori knowledge as to what effect the Nf-κB inhibitors of the present invention would have absent testing of the compounds against each virus in turn. Additionally the papers indicate that the inhibition of Nf-κB may result in a greater risk of LPS-induced shock in septic patients. Finally as Nf-κB is involved in so many different processes it is impossible to predict the effects of Nf-κB inhibition without direct testing of the compounds.

For the reasons cited above the claims are limited as being drawn to a method for treating herpes simplex-1 viral infection or Sendai viral infection by administration of an effective amount of the Nf-κB inhibitor 4-tert-butyldimethylsilyloxy-cyclopent-2-en-1-one.

Genetech, 108 F.3d at 1366 states that "a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion" and "patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable."

Conclusion

No claims are allowable.

The examiner would like to point out that if the applicant's were to draft claims commensurate in scope with the enabled matter set forth above, the claims may be better suited for further consideration. The examiner also wishes to indicate that the

specification is enabling for both enantiomers of 4-tert-butyldimethylsilyloxy-cyclopent-2-en-1-one.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Leonard M. Williams whose telephone number is 571-272-0685. The examiner can normally be reached on MF 9-5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan can be reached on 571-272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

LMW

SREENI PADMANABHAN
SUPERVISORY PATENT EXAMINER